REMARKS

In the Office Action dated October 21, 2003, claims 50, 66, 67, 123 and 126-152 are under consideration. Claims 49, 50, 66, 67, 85, 120-136, and 153-156 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support in the specification. Claims 137-152 and 157-158 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,851,813 to Desrosiers.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 49, 50, 66, 67, 85, 120-136, and 153-156 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support in the specification. The claims are directed to methods of vaccinating individuals against AIDS or AIDS related pathologies by administering vaccine compositions comprising a non-pathogenic HIV-1 isolate carrying deletions in the Nef/LTR coding regions.

The Examiner alleges that the specification fails to demonstrate that other genotypically diverse Nef-deficient HIV-1 isolates would behave in the same manner across a genetically diverse group of people. Relying on Kirchhoff et al. (New Engl. J. Med. 332: 228-232, 1995), Huang et al. (J. Virol. 69: 93-100, 1995) and Michael et al. (J. Virol. 69: 6758-6769, 1995), the Examiner states that the prior art teaches that many viral and host factors contribute to the pathogenicity of any given isolate. Furthermore, the Examiner indicates that the SBBC patients described in the specification were all infected with the same parental virus having a deletion in the *nef*/LTR region. The Examiner contends that it is not clear as to whether the non-pathogenicity feature associated with the HIV isolates obtained from these SBBC patients can be

extended to other HIV-1 isolates, particularly in view of the teaching by Terwilliger et al. (*Proc. Natl. Acad. Sci. USA* 88: 10971-10975, 1991). Terwilliger et al. reported that within the same genetic context, the IIIB *nef* allele slightly retards replication of the virus in a T-cell line, whereas the ELI *nef* allele accelerates replication of the virus.

Applicants observe that that claims 123, 126, 133 and 136 recite specific non-pathogenic isolates, i.e., V94101706, V941031169, and V95031022, respectively, which were obtained from recipients of a parental virus from the same donor. Applicants respectfully submit that the enablement rejection at least should not apply to these claims. Each of the recited isolates has been demonstrated to be non-pathogenic in the respective recipient, and the recipients still remain free of HIV symptoms as of today.

With respect to the remaining claims that are rejected as not enabled, Applicants address the Examiner's contentions as follows. The Examiner contends that the SBBC patients were all infected with the same virus having a deletion in the *nef*/LTR region. Applicants respectfully submit that with donor C18, sequence analysis revealed that the only genetic difference between the virus isolated from C18 and wild-type virus was the deletion corresponding to amino acids 166-206 (nucleotides 9281-9438). This finding demonstrates that the deletion alone is capable of rendering a HIV-1 strain non-pathogenic. Applicants further respectfully submit that, although all other members of the co-hort were infected with a virus containing this deletion, the viruses isolated from these members also contained additional mutations, some of which were common to multiple members of the co-hort, while other mutations were unique to individual members. It is recognized that the viruses isolated from all other members of the co-hort are all genetically diverse, while still remaining non-pathogenic

due to the common deletion in the *nef*/LTR region corresponding to amino acids 166-206 (nucleotides 9281-9438).

The Examiner also contends that the deletion of nucleotides 9281-9438 in the *nef*/LTR region may not be effective at rendering the virus non-pathogenic across genetically diverse people. Applicants respectfully disagree with the Examiner and provide, in **Appendix I**, a summary of the HLA-typing of the SBBC members, which clearly demonstrates that they are genetically diverse form each other.

The Examiner further alleges that the specification fails to demonstrate that the instantly claimed HIV-1 vaccines or therapeutics employing *nef* deletion variants would amount to an efficacious humoral or cellular immune response resulting in the prevention or treatment of HIV infection. The Examiner indicates that the two references we submitted previously, Dyer et al. (1999) and Kent (2001) do not overcome the rejection.

Specifically, the Examiner points out that in Dry et al. (1999), nearly half of the sample population did not appear to have strong HIV-1 specific CTL responses. The Examiner further postulates that the failure to elicit a strong CTL response in these individuals may be due to the fact that a replication-impaired virus that replicates at such a low level would be incapable of producing a robust immune response that would lead to viral inactivation and clearance.

Applicants respectfully submit that in the study conducted by Dyer et al., the donor (D36) and the six recipients were studied for HIV-1 specific cytotoxic T-cell activity by four techniques. Four (D36, C18, C49, C98) of the seven had strong anti-HIV-1 cytotoxic T-cell responses, and one (C135) had no detectable response. It is also known (although not reported in this paper) that all SBBC members, except C135, had strong antibody responses. These results

clearly evidence the effectiveness of the Sydney Blood Bank Cohort (SBBC) strain of HIV-1 in stimulating an immune response in human subjects.

In respect to the claimed compositions, Applicants are not, and should not be, required to show the efficacy of the subject compositions in every individual tested. Especially in the field of AIDS where a vaccine is lacking, a showing that four out of seven patients had strong CTL responses and six out of the seven patients also had antibody responses is strong evidence that the subject compositions have sufficient immunogenicity and can mount effective immune responses in the individuals administered with such compositions.

The Examiner further states that Kent et al. (2001) was published well after the filing date of the instant application and fails to demonstrate that the claimed invention was enabled at the time of filing. In addition, the Examiner contends that Kent et al. employed the SIV macaque model, which cannot be extrapolated to human individuals. The Examiner also contends that Kent et al. employed a construct that contained multiple deletions in both the 5' and 3' Nef/LTR regions and differed significantly from that disclosed claimed by Applicants.

Applicants respectfully submit that the law does not preclude submission of post-filing data that demonstrate that the claimed invention functions in the manner described. In particular, Applicants direct the Examiner's attention to the fact that the techniques employed by Kent et al. in determining the protective effects of the attenuated SIV isolates, including those for measuring the level of plasma SIV RNA and the level of CD4+ lymphocytes techniques, were all available to those skilled in the art at the time the present application was filed.

Furthermore, Applicants respectfully submit that the SIV macaque model is an accepted HIV model of the art. As support of this position, Applicants are providing herewith

Appendix II, which includes an extensive list of publications relating to vaccines, all of which have been published in high impact journals, which have all used the SIV macaque model.

Therefore, Applicants respectfully submit that the teaching in the present specification, combined with the observations made by Dryer et al. with human individuals and the macaque data reported by Kent et al., provide enablement of the claimed vaccine compositions and methods. In view of the foregoing, it is respectfully submitted that the rejection under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

Claims 137-152 and 157-158, drawn to immunogenic compositions and methods of inducing an immune response, are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,851,813 to Desrosiers.

The Examiner states that the '813 patent discloses methods for preparing Nef-deficient HIV-1 proviruses and immunogenic compositions containing such viruses, as well as the use thereof in the induction of immune responses in a host. The Examiner admits that the '813 patent does not disclose deletions in the specific region of Nef as claimed by the present application. Nevertheless, the Examiner contends that the '813 patent clearly illustrates that deletion of the Nef coding portion results in the production of a virus with impaired replicative properties that still retains its immunogenicity. Therefore, the Examiner concludes that it would have been *prima facie* obvious to one skilled in the art to prepare Nef-deficient HIV-1 proviruses and immunogenic compositions, and to administer the compositions to a host to induce a viral-specific immune response. The Examiner states that the immunological reagents generated from the immune response would be useful as diagnostic reagents or for the purification of viral immunogens. The Examiner further states that the precise location of the mutations in the Nef

coding portion is simply a matter of routine experimentation, as long as the resulting mutant virus does not carry a functional *nef* gene.

Applicants respectfully submit that the '813 patent does not teach or suggest making deletions in the specified region of the Nef gene, i.e., corresponding to amino acids 166-206 (nucleotides 9281-9438), as presently claimed. Applicants further respectfully submit that, based solely on the teachings of the '813 patent, those skilled in the art would not have reasonably expected that a deletion in a region of the Nef gene, as recited in the present claims, would result in a virus that is non-pathogenic yet immunogenic. Therefore, it is respectfully submitted that the immunogenic compositions and the methods of claims 137-152 and 157-158, are not obvious based on the '813 patent. Thus, withdrawal of the rejection under 35 U.S.C. §103(a) as allegedly unpatentable over the '813 patent is respectfully requested.

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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Enc.: Appendices I and II